

# Exhibit 59

缬沙坦残留溶剂未知峰研究报告

**Study Report of Unknown Peak in  
Residual Solvent of Valsartan**

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## 报告审批表

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一、研究背景/Background

华海药业缬沙坦残留溶剂（甲醇、乙醇、乙酸乙酯、甲苯）检测方法（华海方法详见附件 1）项下发现存在多个未知峰，典型图谱如图 1。由图 1 可知，此次研究涉及的未知峰共计 9 个，并根据出峰时间依次命名为未知峰\_1~未知峰\_9（未知峰出峰情况表 1）。

Many unknown peaks are identified when tested residual solvent (methonal, ethanol, ethyl acetate, toluene) of Valsartan with Huahai method (For Huahai Analytical method, please refer to Attachment 1), refer to Figure 1 for typical chromatogram. As indicated in Figure 1, there are 9 unknown peaks involved in this study. In the order of their retention time, these peaks are named as unknown peak\_1 to unknown peak\_9 respectively. (For RT of unknown peaks, please refer to Figure 1).

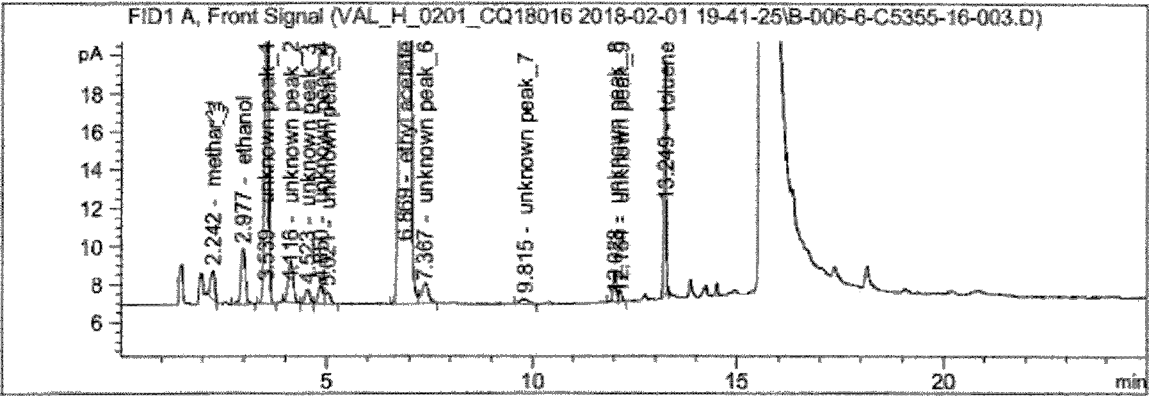


图 1（华海方法典型图谱）

Figure 1 Typical chromatogram of Huahai method

未知峰情况 Unknown peaks	RT (min)	RRT(相对于乙酸乙酯) RRT (relative RT to ethyl acetate)
未知峰_1 Unknown peak_1	3.5	0.51
未知峰_2 Unknown peak_2	4.1	0.59
未知峰_3 Unknown peak_3	4.5	0.65
未知峰_4 Unknown peak_4	4.9	0.71



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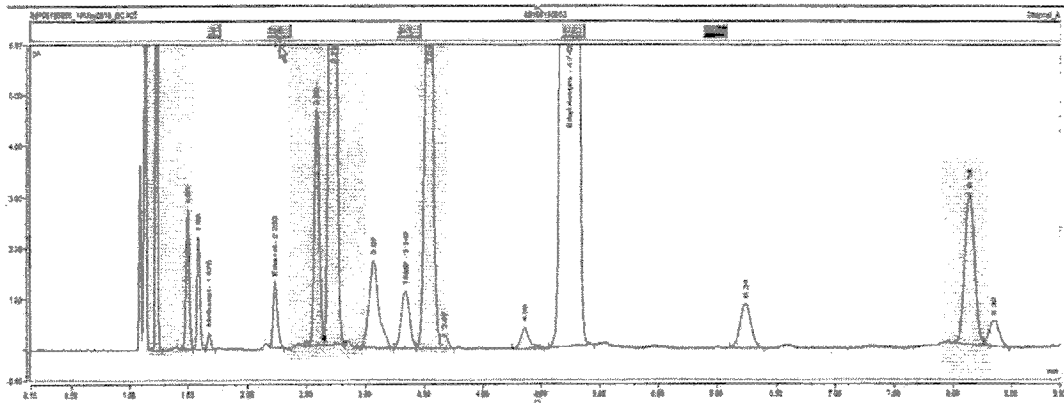
未知峰_5 Unknown peak_5	5.0	0.72
未知峰_6 Unknown peak_6	7.4	1.07
未知峰_7 Unknown peak_7	9.8	1.42
未知峰_8 Unknown peak_8	12.0	1.74
未知峰_9 Unknown peak_9	12.2	1.77

表 1（未知峰出峰情况）

Table 1 RT of each unknown peak

同时诺华客户反馈采用诺华方法（诺华方法详见附件 2）检测缬沙坦残留溶剂，其图谱也存在若干未知峰，典型图谱如图 2：

Feedback was also received from Novartis that when testing residual solvent of Valsartan with Novartis method (Please refer to Attachment 2 for Novartis method), some unknown peaks were also identified. For Typical chromatogram, please refer to Figure 2.







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Based on the huahai's histotical study of unknown solvent peak as well as the study continued after receiving the feedback from Novartis, an overall assessment regarding unknown peaks involved in this study is performed as per ICH as well as Novartis requirement.

## 二、研究目的/Purpose

根据华海药业缬沙坦方法项下残留溶剂未知峰的出峰情况，对其进行鉴别，寻找其最可能的来源，并对这些溶剂进行定量，以评估其残留是否符合 ICH 法规和诺华客户的要求，以及其对产品质量的影响。

Identify unknown peaks (Huahai method) based on their RT, find the most probable source, quantify the solvent corresponding to each peak to see whether the residue comply with ICH and Novartis requirement, to evaluate the impact on product quality.

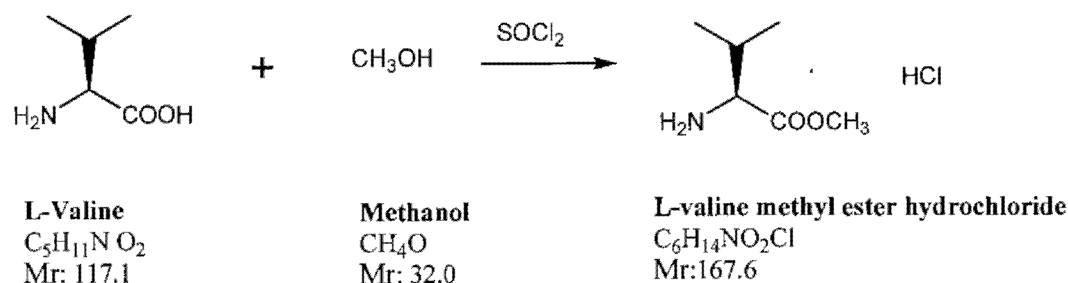
## 三、研究内容/Content

华海药业通过对缬沙坦 ROS (ROS 详见图 3) 的分析，梳理工艺中涉及溶剂（工艺涉及溶剂详见表 2），并借用 GC-MS 解析、GC 定位等手段，对缬沙坦未知峰的鉴别、可能的来源以及定量分析进行研究。

Identify, quantify and find probable source of unknown peaks by analysis of ROS of Valsartan and solvents used in process (Please refer to Table 2 Solvents used in the process), by means of GC-MS and GC RT identification, etc..

### Ros of Valsartan

#### Step 1: Synthesis of L-valine methyl ester hydrochloride







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## 六、研究结论/Conclusion

综上所述，华海药业缬沙坦残留溶剂（甲醇、乙醇、乙酸乙酯、甲苯）检测存在的 9 个未知峰均已确认其来源或可能来源。其中 2 个未知峰（二甲基硫醚和未知峰\_6）确定来源于分析方法，对产品质量无影响。另外 7 个未知峰中能够确定二氯甲烷来源于起始物料的工艺溶剂残留，MTBE 来源于缬沙坦工艺溶剂，乙酸异丙酯、丙酸乙酯、乙酸丙酯来源于缬沙坦工艺溶剂乙酸乙酯，异丁醛和正己烷均未能明确其来源，但异丁醛找到了其最可能的反应机理，正己烷可能来源于溶剂的微量残留，通过定量分析，结果均远远低于指标，用甲苯 10% ICH 标准（89ppm）的峰面积对未知峰进行控制，对产品质量无影响。

From the above, 9 unknown peaks in residue solvents test method (methanol, ethanol, ethyl acetate and toluene) of Valsartan have been identified or the probable source identified. 2 unknown peaks (Dimethyl sulfide and unknown peak \_6) are identified to be introduced by analytical method and there is no impact on product quality. For other 7 unknown peaks, the unknown peak of dichloromethane is introduced by residual process solvent of starting material; MTBE is process solvent of Valsartan; Isopropyl acetate, Ethyl propionate and Propyl acetate are introduced by ethyl acetate (process solvent); the exact source of Isobutyraldehyde and N-hexane are not identified. However, the most probable reaction mechanism of Isobutyraldehyde has been identified. N-hexane may be introduced by trace residue of solvent. The results are far lower than the specification through quantitative analysis. The unknown peaks can be controlled by comparing to the peak area of 10% toluene, ICH limit (89ppm). The product quality is less likely to be impacted.